Insights on mid-term TAVR performance: 3-year clinical and echocardiographic results from the CoreValve ADVANCE study

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**Abstract**

***Background*** Extensive evidence relating to transcatheter aortic valve replacement (TAVR) has accumulated in recent years, but mid-term outcomes are less reported. We investigated 996 patients after implantation of the CoreValve prosthesis for severe aortic stenosis in a real-world setting.

***Objective*** To report clinical and echocardiographic 3-year results from the ADVANCE study.

***Methods*** ADVANCE is a prospective, multicenter, fully monitored, nonrandomized clinical study. This analysis assessed valve-related events, predictors of early and mid-term mortality after TAVR, and systolic and diastolic prosthesis performance over 3 years.

***Results*** Three years after TAVR, the rate of major adverse cardiac/cerebrovascular events was 38.5%. All-cause mortality was 33.7%; cardiovascular mortality, 22.3%; cVARC-1 stroke, 6.5%; and New York Heart Association class III/IV, 19.5%. Mean effective orifice area was consistently 1.7 cm2 from discharge to 3 years, and average mean aortic valve gradient remained ≤10 mmHg. At 3 years, 12.6% of patients had moderate and none had severe paravalvular regurgitation. Multivariable analysis identified Society of Thoracic Surgeons (STS) score, device migration, prior atrial fibrillation, and major vascular complication as predictors of early mortality. Predictors of mid-term mortality included male gender, STS score, history of chronic obstructive pulmonary disease, history of cancer, stroke, life-threatening/disabling or major bleeding, and valve deterioration.

***Conclusions*** Our 3-year data demonstrate significant hemodynamic benefits and durable symptom relief after CoreValve prosthesis implantation. Postprocedural patient management should be carefully considered since postprocedural valve-related events were identified as independent predictors of mid-term mortality.

**Key Words:** transcatheter aortic valve replacement, aortic stenosis, mortality risk, ADVANCE, mid-term outcomes

**INTRODUCTION**

More than 10 years of experience with transcatheter aortic valve implantation (TAVR) has led to a dramatic increase in interventional treatment of severe aortic valve stenosis. A large body of literature demonstrates excellent short-term outcomes with this novel therapy. Acute device success with several different prosthesis types was recently reported as high as 95% and above in large populations [1-3], and 30-day mortality is well below 5% in the most recent series [1-4]. However, mid-term valve performance and valve-related events are less well described. The aim of the ADVANCE study is to investigate a large cohort of nearly 1000 patients after implantation of the Medtronic CoreValve prosthesis for severe aortic stenosis in a real-world setting with annual clinical and echocardiographic follow-up. The current 3-year analysis evaluated the ongoing rate of valve-related events over time, predictors of mid-term mortality in comparison to predictors of early mortality after TAVR, and systolic and diastolic prosthesis performance over time.

**METHODS**

Patients and Device

The ADVANCE trial is a prospective, multicenter, fully monitored, nonrandomized clinical study of 1,015 patients undergoing TAVR conducted at 44 sites in 12 countries. Briefly, patients who were inoperable or at high surgical risk and also had severe symptomatic aortic stenosis met criteria for enrollment. The only exclusion criteria were current enrollment in another trial or unwillingness or inability to provide written informed consent. The protocol was approved by the ethics committee at each site and conducted in adherence to the Declaration of Helsinki. All patients provided consent. The self-expanding CoreValve System (Medtronic, Minneapolis, MN) was utilized in this study. During the time period of the study, the 26- and 29-mm valve sizes were available. The heart team at each center made sizing and procedural decisions. The study has been described in detail elsewhere [5].

Endpoints

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) at 30 days postprocedure [5], defined as the composite of all-cause mortality, myocardial infarction, stroke, or reintervention. Safety endpoints at 3 years post procedure are reported here, and include MACCE, the individual components, New York Heart Association (NYHA) functional class, and echocardiographic outcomes.

Study oversight

The study protocol and case report forms were designed by the study steering committee and the sponsor (Medtronic). The study is fully monitored, and adverse endpoints were adjudicated according to Valve Academic Research Consortium (VARC-1) [6] definitions by an independent clinical events committee comprised of cardiac surgeons and interventional cardiologists. The committee used an independent neurologist’s assessment, along with other available patient source data, to adjudicate the events. Electrocardiograms and angiograms were assessed by a core laboratory (Cardialysis, Rotterdam, The Netherlands). Aortic regurgitation (AR) was measured by angiography immediately postprocedure and by transthoracic echocardiography at the implanting sites during follow-up visits. The classifications of the European Association of Echocardiography (none, mild, moderate, or severe) were followed [7].

Statistical analysis

Continuous variables are reported as the mean±standard deviation (SD). Categorical variables are reported as the number and percentage. Clinical outcomes are reported as Kaplan-Meier estimates, and freedom from event curves were generated using the Kaplan-Meier method. The log-rank test was used to test for differences across groups. Logistic regression analysis was used to evaluate the association of AR at discharge with worsening NYHA from 2 to 3 years. A paired t test was used to evaluate the change in mean gradient (MG) and effective orifice area (EOA) between time periods. For paired NYHA and paravalvular leak (PVL) data, an overall p value for differences was calculated using Bowker’s test of symmetry, while p values for individual paired comparisons were calculated using McNemar’s test. For the predictors of mortality analysis, Cox proportional hazards model was used for the univariable and multivariable analysis. Factors for inclusion in the univariable model were identified based on clinical judgment. Events that occurred in ≤5% of patients were excluded. All variables identified in the univariable analysis with P<0.20 were entered into the stepwise selection process with a stay criterion of P<0.10 in the final multivariable model. Additional details are listed in the Supplement.

**RESULTS**

Patient and Procedural Characteristics

Patient and procedural characteristics from the ADVANCE study were described previously [5]. Briefly, 1,015 patients were enrolled from March 2010 to July 2011; Of 996 patients attempted treatment, mean follow-up duration was 29.6 ± 14.6 months. Mean age was 81.1±6.4 years and mean logistic EuroSCORE, 19.4±12.3% (Table 1). The iliofemoral approach was the most common access route (88.4%); the subclavian (9.5%) and direct aortic (2.1%) routes also were used. General anesthesia was used in 44.7% of cases [5].

Clinical Outcomes

MACCE increased from 8.0% at 30 days to 38.5% at 3 years (Table 2). All-cause mortality was 33.7%, and cardiovascular mortality was 22.3% (Fig 1A). The freedom from all-cause mortality rate differed significantly when stratified by logistic EuroSCORE (Fig 1B) and by total aortic regurgitation at discharge (Figure 1C). The VARC-1 stroke rate was 6.5% (Fig 1D).

NYHA Class

The proportion of patients in NYHA class III or IV at 1 month was 15.7%, compared with 19.5% at 3 years (Fig 2). A paired analysis (N=483) demonstrated a significant (P<0.001) overall improvement in NYHA class at all follow-up points compared to baseline. There were no significant differences in NYHA between 1 month and 1 or 2 years, but a significant difference was seen between 1 month and 3 years (P<0.001). This was driven mainly by more patients moving into class III or IV at 3 years as compared to 1 month.

Valve Hemodynamics

Three year echo compliance was 67%; 891 subjects had discharge TTE performed, and 806 subjects had at least 1 follow-up TTE performed after the discharge until 3 years. Mean EOA was consistently 1.7 cm2 from discharge to 3 years postprocedure for patients with data available at each time point (Fig 3A). MG also improved from 45.6 mmHg at baseline to 9.8 mmHg at discharge, and was 9.0 mmHg 3 years postprocedure for patients with data available at each time point.

 In paired analyses of valve hemodynamic data (N=89 EOA and N=166 MG), both EOA and MG significantly improved from baseline to 3 years (P<0.001), with EOA ranging from 1.8 cm2 at discharge to 1.7 cm2 at all remaining follow-up visits, and MG ranging from 9.9 mmHg at discharge to 9.1 mmHg at 3 years. Valve hemodynamics were plotted according to the last valve size implanted (Fig 3B). Average MG was ≤10 mmHg for both valve sizes from discharge to 3 years, and similar EOAs were observed*.*

Paravalvular Regurgitation

Postprocedural PVL remained relatively unchanged throughout follow-up (Fig 4). A paired analysis of 208 patients revealed 1 patient with severe PVL at 1 month, but none at any other follow-up visit; the percentage of patients with moderate PVL (13.5%) remained consistent at 2 and 3 years (P=0.85 3 years vs. discharge). The percentage of patients with mild PVL decreased from 62.0% at discharge to 44.2% at 3 years (P<0.001), and the percentage with no PVL increased from 25.0% at discharge to 42.3% at 3 years (P<0.001).

Valve hemodynamics and NYHA Class

Among patients with worsened NYHA class from 2 to 3 years after TAVR (N=129), there was a similar distribution of AR (none 20.9%, mild 65.9%, moderate 13.2%) compared to patients with same or improved NYHA class (N=404; none 22.5%, mild 64.6%, moderate 12.9%). Logistic regression analysis revealed no significant association between severity of AR at discharge and NYHA class evolution [P=0.93; Mild vs. none = O.R: 1.10 (95%: 0.68, 1.80); Moderate vs. none = 1.10 (0.55, 2.21); Mild vs. moderate = 1.00 (0.55, 1.82).

Predictors of Mortality

*Early (30 days)*

Variables identified through the stepwise selection process are listed in the online supplement. Multivariable analysis revealed STS score, device migration, prior atrial fibrillation, and major vascular complication as predictors of early mortality after TAVR (Table 3).

*Mid-term (31-1095 days)*

There were 950 subjects in the risk set at 31 days postprocedure. Most patients excluded from the stepwise selection process were missing data for AR at discharge. The final model included male gender, STS score, history of chronic obstructive pulmonary disease, history of cancer, stroke (VARC-1 criteria), life-threatening/disabling bleeding or major bleeding, and valve deterioration (structural or non-structural) as predictors of mid-term mortality (Table 3).

**DISCUSSION**

The 3-year analysis of the ADVANCE study revealed a low incidence of valve-related events (VARC-1), that predictors of mid-term mortality include preexisting comorbid conditions and valve-related events, and that clinical and hemodynamic improvement are maintained after TAVR with the CoreValve prosthesis.

These data demonstrate that surviving patients are likely to be largely symptom-free within 2 to 3 years after TAVR. Events like myocardial infarction, emergent reintervention, stroke, and life-threatening or major bleeding or vascular complications are rare between 30 days and 3 years. The Kaplan-Meier event rates of these events increased slightly (<4%) between 30 days and 3 years. The new pacemaker rate at 3 years of 31.4% is slightly higher than the 28% reported in the CoreValve US Pivotal High Risk Trial [8], and considerably higher than that reported with self-expanding devices [9,10]. However, newer generation devices have since been developed, and clinical best practices with the self-expanding system have greatly reduced the inicidence of conduction disturbances [11,12]. NYHA class is improved at all time points compared with baseline. However, between 2 and 3 years after TAVR, some patients exhibit worsened NYHA class. While >80% of patients are in NYHA class I or II after 3 years, the proportion of patients in classes III and IV increases by 3 years as compared with 30 days postprocedure. PVL was clearly excluded as an influencing factor for worsened NYHA class (P=0.93). But considering the advanced age and comorbidities of the patients, it is reasonable to speculate that this finding is multifactorial. A similar continuous increase in patients exhibiting worse NYHA class has been shown in an early single-center experience [13].

While the frequency of valve-related events is low over time, there is a continuous decline in survival with the majority of patients dying of cardiovascular causes. At 3 years post-TAVR, we observed a survival rate of 66.3% and a freedom from cardiovascular death rate of 77.7%. These rates are comparable to those reported by others at 3 years (54.9% all-cause mortality and 41.4% cardiovascular mortality in the PARTNER trial [9], 38% all-cause mortality after CoreValve device implantation by Barbanti et al [14], 38.8% all-cause mortality in the UK TAVI Registry [15], 34.8% all-cause mortality and 12.5% cardiovascular mortality in the Italian Registry [16], and 42.0% all-cause mortality and 17.5% cardiovascular mortality in the France-2 registry) [17]. Recently, the CoreValve High Risk US Pivotal Trial reported 32.9% all-cause mortality and 22.9% cardiovascular mortality at 3 years in TAVR patients [8].

 In a previous report from the ADVANCE study, predictors of all-cause mortality at 1 year included stage III acute kidney injury and moderate or severe AR at discharge [5]. The present study has expanded on this to identify predictors of early (0-30 days) and mid-term (31-1095 days) mortality. It is clear that baseline variables, including STS score and prior atrial fibrillation, as well as severe procedural complications, like device migration or major vascular complications, significantly impact early death within 30 days after the TAVR procedure. Similarly, mid-term mortality is influenced both by baseline comorbidities, such as chronic obstructive pulmonary disease or cancer (as also reflected by STS score), and by complications during follow-up, like strokes or bleeding events [18]. An early multicenter analysis from Italy reported prior stroke, postprocedural PVL ≥2+, prior acute pulmonary edema, and chronic kidney disease as predictors of mortality between 30 days and 1 year [19]. Recently, Arnold et al reported several predictors of poor outcomes (composite of mortality and reduced quality of life scores) at 6 months and 1 year, including serum creatinine, oxygen-dependent lung disease, mean aortic valve gradient, Mini-Mental State Examination score, and 6-minute walk test distance [20]. Other reports have identified similar predictors of mid- or long-term mortality (>30 days), including age, body mass index, creatinine >200 µg/mmol (renal disease), albumin >3.3 g/dl, liver disease, smoking, atrial fibrillation, chronic obstructive pulmonary disease, prior stroke, left ventricular ejection fraction, logistic EuroSCORE, STS score, and frailty measures such as home oxygen use, falls within the past 6 months, Charlson scores, and assisted living [15,21-27]. A 2010 multicenter report from Canada also identified periprocedural sepsis or need for hemodynamic support and pulmonary hypertension as predictors of cumulative late mortality and noted that frailty did not appear to impact outcomes [28]. Coronary artery disease has also been associated with increased mortality after TAVR [29].

Despite a low 30-day mortality of 4.5% in a TAVR cohort with a mean logistic EuroSCORE of 19.4% at baseline, the mortality event rate was 33.7% at 3 years. Detailed knowledge of predictors for mid- or long-term death after TAVR may improve postprocedural management, eg, antiplatelet or anticoagulation therapy to influence occurrence of stroke and bleeding events, which were identified as independent predictors of mid-term mortality up to 3 years in the current study. Previous data from the ADVANCE study indicate that the overall stroke rate was low and that predictors of neurological events differ depending on whether the events were periprocedural, early, or late [30].

Both sizes of the CoreValve prosthesis exhibited exceptionally low gradients of no more than 10 mmHg, with no change in mean EOA or MG up to 3 years after TAVR, demonstrating that hemodynamic deterioration is not significantly occurring within that time period. Five-year data from the PARTNER trial have also shown unchanged systolic valve function [31]. Longer term studies will have to be conducted to address this subject.

 The frequency of moderate PVL was statistically unchanged from discharge to 3 years using paired data and was 13.5% at 3 years with this first-generation TAVR device. Severe leaks occurred in ≤0.6% at any time point. Multiple studies have demonstrated an important impact of PVL on survival after TAVR. Indeed, the presence of severe total AR at discharge has been associated with increased late mortality [32], and PVL that is mild or greater was identified as a strong univariate predictor of mortality following TAVR [33]. Postprocedural AR of grade 2 or higher (but not grade 1) was a strong independent predictor of 1-year mortality for both self-expandable and balloon-expandable TAVR devices [34]. Several articles have indicated that even mild PVL was associated with increased late mortality [35,36]. However, data on the impact of mild AR after TAVR is mixed, possibly due to challenges in assessing and quantifying AR after TAVR [37]. The ADVANCE study data show a significant impact of moderate or severe AR at discharge on mid-term mortality in the univariable analysis, but it was not identified as an independent predictor of early or mid-term mortality in the multivariable analysis. It is likely that other comorbid factors become more important in the longer term. Data from another subanalysis of the ADVANCE study demonstrate that moderate or severe AR has a more significant impact on mortality in patients with a lower (<7%) STS score risk profile, and thus with less comorbidities [14]. Nevertheless, there is consensus that PVL after TAVR should be avoided. This was addressed by most of the newer generation TAVR devices. An early series of the successor model of the CoreValve prosthesis, the Evolut R device, showed a reduced rate of moderate or severe AR of 6.7% [3].

Limitations

The total number of TAVR cases performed at the centers was larger than the number of patients who entered the ADVANCE study, and some received other transcatheter valves. This was due to anatomical factors or to the decision of the patient and the physician. Therefore, like in any other trial, we cannot exclude that a selection bias may have influenced the results, and we are unable to report data from these patients treated outside the ADVANCE study. In addition, the evaluation of AR by echocardiography postprocedure was performed locally in the absence of a central echocardiographic core laboratory, which might have induced bias as well. Echocardiographic follow up at 3 years was also limited to only 20% of patients. ADVANCE was not a randomized trial, and cases were selected by a heart team. However, the study reflects expert clinical practice in real-world patients.

**CONCLUSIONS**

As TAVR indications are clearly expanding to additional patient populations, knowledge on mid- and long-term outcomes becomes paramount. Three-year data from ADVANCE demonstrated that patients may expect significant and durable symptom relief after interventional treatment of severe aortic stenosis with a low rate of valve-related events over time. In this “real-world” TAVR population with multiple comorbidities, there was a continuous decrease in survival over 3 years. Preexisting comorbid conditions as well as late valve-related events were identified as independent predictors of mid-term mortality. Accordingly, postprocedural management to address independent predictors of mortality, eg, antiplatelet or anticoagulation therapy to prevent stroke and bleeding events, may be adopted. Further studies are needed to clarify these questions. The ADVANCE study showed a durable hemodynamic benefit after CoreValve prosthesis implantation with consistent valve functioning, as shown by EOA, MG, and PVL.

**Conflict of interest:** Dr. Bleiziffer has served as a consultant and proctor for Medtronic, a proctor for JenaValve, a proctor for Boston Scientific, and has received travel expenses from Medtronic. Dr. Bosmans serves as a proctor for Medtronic. Dr. Brecker has received consultant fees from Medtronic and Boston Scientific. Dr. Gerckens has received consulting and lecture fees and study-related travel expenses from Medtronic and Edwards Lifesciences, and serves as a proctor for Medtronic and Boston Scientific. Dr. Wenaweser has received consulting fees from Medtronic and Edwards Lifesciences, and has received remuneration from Medtronic for study-related travel and for development of educational materials. Dr. Tamburino has no relevant relationships to disclose. Dr. Linke has received speaker honoraria or served as a consultant for the following companies: Medtronic, St. Jude Medical, Claret Medical Inc., Boston Scientific, Edwards Lifesciences, Symetis, and Bard, and holds stock options from Claret Medical Inc. In addition, he received grant support from Medtronic and Claret Medical Inc.

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**FIGURE LEGENDS**

**Fig. 1** Freedom from (a) all-cause mortality and cardiovascular mortality, (b) all-cause mortality stratified by logistic EuroSCORE, (c) all-cause mortality stratified by total aortic regurgitation at discharge, and (d) all stroke.

**Fig. 2** NYHA symptom status for (a) all patients and (b) those with paired data available P<0.001).

**Fig. 3** Valve hemodynamics over time for the overall cohort (a). Paired data (N=89 EOA and N=166 MG), demonstrated significant improvements from baseline to 3 years (P<0.001) for both EOA and MG. Valve hemodynamics according to the last valve size used (b).

**Fig. 4** Paravalvular leak for (a) all patients and (b) those with paired data available, discharge vs. 3 years: P<0.001).

**Table 1. Baseline Demographics**

|  | N=1015 |
| --- | --- |
| Age (y) | 81.1±6.4 |
| Male | 501/1015 (49.4) |
| Logistic EuroSCORE (%) | 19.4±12.3 |
| NYHA class III/IV | 794/997 (79.6) |
| Diabetes mellitus | 315/1003 (31.4)  |
| Coronary artery disease | 585/1012 (57.8) |
| Peripheral vascular disease | 198/1006 (19.7)  |
| Atrial fibrillation | 336/1006 (33.4)  |
| Left ventricular ejection fraction (%) | 53.3±13.7 |
| Previous myocardial infarction | 162/990 (16.4)  |
| Percutaneous coronary intervention | 316/1004 (31.5)  |
| Previous permanent pacemaker placement  | 131/1015 (12.9)  |
| Coronary artery bypass surgery  | 217/1011 (21.5)  |
| Cerebrovascular disease | 131/998 (13.1)  |
| Chronic obstructive pulmonary disease | 229/1011 (22.7)  |
| Pulmonary hypertension\* | 127/968 (13.1)  |
| Renal failure† | 148/996 (14.9)  |

\*Pulmonary systolic pressure >60 mmHg. †Creatinine clearance <20 mL/min. Values are presented as no./total no. (%) or mean±SD.

**Table 2. Clinical Outcomes**

|  |  |  |
| --- | --- | --- |
|  | 30 Days(N=996) | 3 Years(N=996) |
| MACCE (VARC-1) | 8.0 (80) | 38.5 (373) |
|  All-cause mortality | 4.5 (45) | 33.7 (325) |
|  Myocardial infarction | 0.2 (2) | 2.6 (21) |
|  Emergent cardiac surgery/percutaneous re-intervention | 1.3 (13) | 2.4 (21) |
|  Stroke | 3.0 (30) | 6.5 (57) |
|  Major stroke | 1.2 (12) | 3.5 (30) |
| Transient ischemic attack | 0.4 (4) | 2.1 (18) |
| Cardiovascular mortality | 3.4 (34) | 22.3 (202) |
| Bleeding | 29.0 (288) | 35.3 (338) |
|  Life-threatening or disabling | 4.0 (40) | 6.1 (56) |
|  Major | 9.7 (96) | 12.7 (121) |
| Vascular complications | 20.7 (206) | 22.0 (217) |
|  Major | 10.9 (108) | 12.3 (120) |
| Acute kidney injury, stage III | 0.4 (4) | 0.6 (6) |
| New pacemaker implantation (baseline included) | 26.3 (259) | 31.4 (300) |
| Repeat/prolonged hospitalization | 26.0 (255) | 68.4 (636) |
| Death or repeat/prolonged hospitalization | 28.6 (285) | 73.4 (722) |

Values are Kaplan-Meier event rates (no. of patients with events).

**Table 3. Multivariable Predictors of Mortality (Early and Mid-term) Post-TAVR**

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **Hazard Ratio** | **95% Confidence Interval** | **P-Value** |
| **Early (0-30 d) mortality** |
| STS mortality score |  |  | 0.07 |
|  4-8% vs. <4% | 1.44 | 0.63-3.28 | 0.39 |
|  <4% vs. >8% | 0.39 | 0.17-0.92 | 0.03 |
|  >8% vs. 4-8% | 1.77 | 0.92-3.40 | 0.09 |
| Device migration/reposition with snare\* | 3.45 | 1.81-6.58 | <0.001 |
| Prior atrial fibrillation† | 1.67 | 0.92-3.03 | 0.09 |
| Major vascular complication | 2.71 | 1.34-5.48 | 0.01 |
| **Mid-term (31-1095 d) mortality** |
| Male | 1.31 | 1.03-1.67 | 0.03 |
| STS mortality |  |  | <0.001 |
|  4-8% vs. <4% | 1.08 | 0.80-1.45 | 0.63 |
|  <4% vs. >8% | 0.54 | 0.39-0.75 | <0.001 |
|  >8% vs. 4-8% | 1.73 | 1.31-2.30 | <0.001 |
| Chronic obstructive pulmonary disease | 1.48 | 1.14-1.93 | 0.004 |
| Cancer | 1.56 | 1.18-2.05 | 0.002 |
| Stroke (VARC) | 3.05 | 1.98-4.71 | <0.001 |
| Life-threatening, disabling, or major bleeding | 1.89 | 1.43-2.51 | <0.001 |
| Valve deterioration (structural or nonstructural)£ | 1.70 | 1.10-2.63 | 0.02 |

Full details of this analysis provided in the online supplement.

\*Device migration observed, reposition with snare, valve-in-valve, valve retrieval, or valve dislocation at the procedure.

†History of atrial fibrillation or atrial fibrillation reported at baseline.

£Structural deterioration includes trial valve dysfunction or deterioration, exclusive of infection or thrombosis, as determined by reoperation, autopsy, or clinical investigation; The term refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, stent creep, or suture line disruption of components of a trial valve.